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Comparison of Yuzpe regimen, danazol, and mifepristone (RU486) in oral postcoital contraception

Anne M C Webb, Jean Russell, Max Elstein

Abstract

***Objective*—To compare the effectiveness and acceptability of three regimens of postcoital contraception.**

***Design*—Randomised group comparison of ethinyloestradiol 100 μg plus levonorgestrel 500 μg repeated after 12 hours (Yuzpe method); danazol 600 mg repeated after 12 hours; and mifepristone 600 mg single dose.**

***Setting*—Community family planning clinic.**

***Subjects*—616 consecutive women with regular cycles aged 16 to 45 years.**

***Main outcome measures*—Number of pregnancies, incidence of side effects, and timing of next period.**

***Results*—The raw pregnancy rates (with 95% confidence intervals) for the Yuzpe, danazol, and mifepristone groups were 2·62% (0·86% to 6·00%), 4·66% (2·15% to 8·67%), and 0% (0% to 1·87%) respectively. Overall, these rates differed significantly (χ^2=8·988, df=2; p=0·011). The differences between the mifepristone and Yuzpe groups and between the mifepristone and danazol groups were also significant. Side effects were more common and more severe in the Yuzpe group (133 women (70%)) than in either the danazol group (58 (30%)) or the mifepristone group (72 (37%)). The Yuzpe regimen tended to induce bleeding early but mifepristone prolonged the cycle. Three women bled more than seven days late in the Yuzpe group compared with 49 in the mifepristone group.**

***Conclusions*—Mifepristone was effective in reducing expected pregnancy rates and the Yuzpe method also had a clinical effect. Danazol had little or no effect. A further multicentre trial is needed.**

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Introduction

Many methods of postcoital contraception have been used. Postcoital oestrogen given for five days was first introduced in the 1960s and was widely used.[1,2] The failure rate was between 0·5% and 1·6% and side effects of nausea, vomiting, and breast tenderness were common. Yuzpe *et al* later combined oestrogen and progestogen given over 12 hours. This achieved a 125-fold reduction in the dose of oestrogen, and the intensity and duration of side effects were reduced.[3] Failure rates between 1·7% and 2·3% have been found.[3,4]

A comparative study showed similar effectiveness to oestrogen treatment and suggested the Yuzpe regimen was preferable because of the shorter duration of treatment.[5] Estimating the numbers of expected pregnancies is difficult but a reduced incidence has been shown when compared with numbers predicted by various methods.[2,6-9] The Yuzpe regimen has become an accepted and recommended method of postcoital contraception.[10]

Danazol has been suggested to be as effective as the Yuzpe method with fewer side effects.[11,12] The antiprogesterone drug mifepristone has been shown to be an effective abortifacient and has been used as an interceptive and menstrual regulator,[13-15] although it causes considerable cycle upset.[16,17] We conducted a study to compare the effectiveness and side effects of these three methods (Yuzpe, danazol, mifepristone).

Subjects and methods

Women requesting emergency contraception after only one act of unprotected intercourse during their current cycle were considered for study if they presented within 72 hours of the act. Only women with regular cycles were included. The length of the cycle could vary from 21 to 35 days, but for one individual the variation over the previous three months could not exceed four days. Women who had been pregnant in the previous three months were excluded. The study was restricted to women who were aged 16-45 years, willing to sign consent, and available for follow up. Women with contraindications to oestrogen or progestogen (thromboembolic disease, liver disease, breast cancer, diabetes, jaundice, or pruritus of pregnancy), with known or suspected adrenal disease, or who were taking interacting drugs (liver enzyme inducers, broad spectrum antibiotics) were excluded. No woman had taken any sex steroids since her last menstruation. All women were interviewed by the same person (AMCW).

The date of the last menstruation, cycle length, and exact time of unprotected intercourse were noted. Any use of contraception (coitus interruptus, failed barrier), height, weight, and previous pregnancies and their outcome were recorded. Serum progesterone concentration was measured by quantitative radioimmunoassay.

Subjects were randomly allocated to receive the Yuzpe regimen (ethinyloestradiol 100 μg and levonorgestrel 500 μg repeated after 12 hours), danazol 600 mg repeated after 12 hours, or mifepristone 600 mg one dose only. The allocation schedule was constructed by using a computer based pseudorandom number generator with a uniform distribution. The schedule was prepared before the start of the study by JR, who did not participate in either the selection or assessment of women. The mifepristone was always taken in the clinic. The other two drug regimens were also always started within 72 hours of unprotected intercourse but the first dose was often taken after the visit to the clinic to obviate taking the tablets on an empty stomach or

having to wake up in the middle of the night for the second dose.

Each woman was given a diary card on which to record any vaginal bleeding, nausea, vomiting, breast tenderness, any other side effects, and concomitant drugs. She was seen again just after her next menstruation was expected (taking into account her last bleed and cycle length) and the date and amount of bleeding were recorded. If pregnancy was suspected serum was taken to measure β human chorionic gonadotrophin concentration by quantitative radioimmunoassay. If the result was positive the various options, including termination of pregnancy, were discussed.

The study was approved by the local (South Manchester District Health Authority) and World Health Organisation ethics committees.

STATISTICAL METHODS

A pregnancy rate of 7% was assumed in the absence of postcoital treatment.[2] Pregnancy rates of around 2% are most commonly reported for the Yuzpe method.[18] Power calculations showed that 356 patients would be required to show this difference to be significant at the conventional 5% level with 90% power for two groups. We adopted a sample size of 1200 to compensate for the addition of a third group. A preplanned interim analysis at 600 completed patients showed that some of the treatment differences were much greater than expected and it was considered unethical to continue the study. Patients currently in the study were followed up, giving a total sample size of 616.

The proportions of women in each treatment group experiencing appropriate clinical events were calculated with 95% confidence intervals where indicated.[19] For each treatment group pregnancy rates and standardised ratios (number of observed pregnancies divided by number expected) were computed with 95% confidence intervals.[19] Various methods of estimating risk of pregnancy have been suggested.[2,6-9] We used the risk tables of Dixon *et al*, who combined the different estimates to produce a risk for each day of the cycle.[2]

Results

A total of 616 women were recruited: 27 (4·4%) were lost to follow up or had unusable results and 23 (3·7%) women had a partial follow up. This group included women who had been followed up very late (for whom the only information available was that they had not been pregnant) and women who had had further acts of unprotected intercourse in the cycle (who had taken further postcoital contraception). In the last group side effects could be assessed but not effectiveness or date of

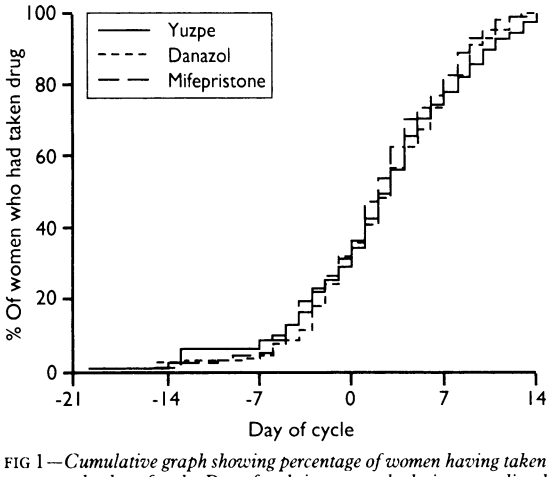

FIG 1—*Cumulative graph showing percentage of women having taken treatment by day of cycle. Day of cycle is expressed relative to predicted day of ovulation, which was calculated by adding usual cycle length to day of last menstrual period and subtracting 15*

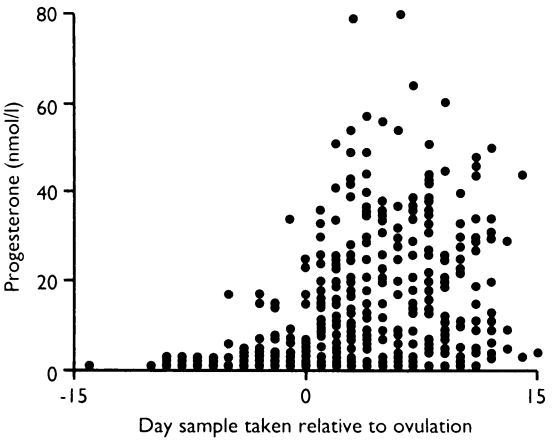

FIG 2—*Progesterone concentration at time of clinic visit relative to estimated day of ovulation*

next period. None of these women became pregnant. Consequently, the occurrence of pregnancy could be assessed in 579 (94%) women, the incidence of side effects in 581 (94%) women, and the timing of the next bleed in 566 (92%).

Table I shows the characteristics of the women and type of contraception used, if any.

TABLE I—*Method of contraception, previous proved fertility, and age of women for whom it was possible to assess effectiveness of treatment*

	No (%) receiving Yuzpe regimen	No (%) receiving danazol	No (%) receiving mifepristone
Method of contraception used:			
None	54 (28)	62 (32)	56 (29)
Sheath	133 (70)	119 (62)	130 (67)
Coitus interruptus	2 (1)	11 (6)	7 (4)
Other	2 (1)	1 (1)	2 (1)
Fertility proved:			
No	140 (73)	142 (74)	133 (68)
Yes	51 (27)	51 (26)	62 (32)
Age range (years):			
16-20	64 (34)	63 (33)	60 (31)
21-25	69 (36)	78 (40)	78 (40)
26-30	40 (21)	30 (16)	35 (18)
31-35	12 (6)	11 (6)	14 (7)
≥36	6 (3)	11 (6)	8 (4)
Total	191	193	195

Most women (412) were under 25 years old. The young age of most women was also reflected in the large number (415) who had never been pregnant. Two thirds of the women had used a barrier which had failed. Although a few had used diaphragms, most had used sheaths which had split or come off.

Figure 1 shows the timing of taking postcoital contraception relative to the time of expected ovulation. The distribution was similar in all three treatment groups. Figure 2 shows the serum progesterone concentrations at presentation. They were consistent with the time of the cycle as calculated by the date of the last period and cycle length.

PREGNANCIES

The probability of pregnancy calculated from estimates published by Dixon *et al*[2] predicted 34·7 pregnancies overall; 14 were observed (table II).

Only five pregnancies occurred in the Yuzpe group, in which 11·3 were predicted. One woman had had intercourse the day before predicted ovulation using a sheath. Four women had used no contraception: two had had intercourse on the day of expected ovulation, one two days after expected ovulation, and one three days after.

In the danazol group 11·7 pregnancies were predicted and nine observed. Six of these women had used a sheath. Two pregnancies were conceived late in the cycle: one women later admitted to sometimes having a

TABLE II—*Expected and observed numbers of pregnancies according to treatment group and day of unprotected intercourse*

Day of cycle*	Probability of pregnancy	Yuzpe			Danazol			Mifepristone		
		No of women	Expected	Observed	No of women	Expected	Observed	No of women	Expected	Observed
<−8	0·000	5	0·000	0	2	0·000	0	5	0·000	0
−8	0·001	6	0·006	0	6	0·006	0	3	0·003	0
−7	0·007	3	0·021	0	3	0·021	0	4	0·028	0
−6	0·025	9	0·225	0	4	0·100	0	11	0·275	0
−5	0·055	11	0·605	0	13	0·715	0	7	0·385	0
−4	0·104	8	0·832	0	11	1·144	1	9	0·936	0
−3	0·146	8	1·168	0	12	1·752	0	9	1·314	0
−2	0·169	5	0·845	0	11	1·859	0	6	1·014	0
−1	0·173	13	2·249	1	9	1·557	1	16	2·768	0
0	0·141	23	3·243	2	15	2·115	0	15	2·115	0
1	0·091	10	0·910	0	16	1·456	3	23	2·093	0
2	0·049	18	0·882	1	15	0·735	1	7	0·343	0
3	0·019	14	0·266	1	11	0·209	1	19	0·361	0
4	0·005	6	0·030	0	11	0·055	0	9	0·045	0
5	0·001	8	0·008	0	11	0·011	0	10	0·010	0
>5	0·000	44	0·000	0	43	0·000	2	42	0·000	0
Total		191	11·290	5	193	11·735	9	195	11·690	0
Pregnancy rate (95% confidence interval)		2·62 (0·86 to 6·00)			4·66 (2·15 to 8·67)			0·00 (0·00 to 1·87)		
Standardised ratio (95% confidence interval)		0·443 (0·144 to 1·030)			0·767 (0·351 to 1·460)			0·000 (0·000 to 0·316)		

*The day of the cycle is expressed relative to the day of expected ovulation (day 0). This was calculated by adding the usual cycle length to the day of last menstrual period and subtracting 15.

longer cycle, but the other apparently conceived on day 24 of a regular 28 day cycle.

In the mifepristone group 11·7 pregnancies were predicted. No clinical pregnancies were observed, though one woman had a β human chorionic gonadotrophin concentration of 149 IU/l 19 days after unprotected intercourse. The concentration fell spontaneously and she bled 14 days late. An endometrial biopsy showed decidual reaction but no chorionic villi.

Five other pregnancies were observed which were not conceived at the time of the unprotected intercourse. Two women were pregnant when presenting despite having had a bleed at the expected time within the previous three weeks. This was confirmed by the finding of β human chorionic gonadotrophin concentrations above 500 IU/l in the blood sample taken to measure progesterone at presentation. One woman took mifepristone and at the follow up visit four weeks later had a β human chorionic gonadotrophin concentration of 21 IU/l. She had a heavier than normal bleed 30 days after treatment. The second woman took the Yuzpe regimen and her pregnancy continued.

Three women, all in the mifepristone group, conceived between the time of treatment and the follow up visit, one about 10 days after and two about 15 or 16 days after the reported date of unprotected intercourse. All women had been urged to use adequate contraception in the immediate future as the treatment given could give cover only for the previous 72 hours. The three women who conceived after mifepristone treatment said they had subsequently used sheaths with no obvious problems.

Delayed conception was suspected when the concentration of chorionic gonadotrophin at the follow up visit was less than expected for a normal pregnancy conceived at the time of the reported unprotected intercourse.[20] By repeating the measurement and obtaining one or more ultrasound scans, normal pregnancies conceived later than the reported date were confirmed. One of these women had a very light bleed three days after taking mifepristone and her chorionic gonadotrophin concentration and ultrasound scan agreed with a normal conception two weeks after this bleed. The other two reported no bleeding. As these three pregnancies were clearly not conceived at the time of the reported unprotected intercourse they cannot be considered failures of the mifepristone treatment and have been excluded from the analysis.

PREGNANCY RATES

The raw pregnancy rates (with 95% confidence intervals) for the Yuzpe, danazol, and mifepristone groups were 2·62% (0·86% to 6·00%), 4·66% (2·15% to 8·67%), and 0% (0% to 1·87%) respectively. Overall these rates differed significantly ($\chi^2=8·988$, df=2; p=0·011). Breaking this test down into a series of pairwise comparisons showed a non-significant difference between the mifepristone and Yuzpe groups (p=0·061) and a significant difference between the mifepristone and danazol groups (p=0·004). Although the failure rate in the danazol group was nearly twice that in the Yuzpe group, the difference was not significant at the conventional level.

A comparison of raw pregnancy rates takes no account of expected rates. Standardised ratios were therefore calculated for the three groups (table II). These rates cannot be formally compared because no pregnancy was observed in the mifepristone group, but the findings for raw pregnancy rates are clearly replicated. The standardised ratios show that the number of observed pregnancies in the danazol group did not differ significantly from the number of expected pregnancies if no treatment had been given. There was a significant difference from the expected number for the mifepristone group (p<0·001) and a significant difference for the Yuzpe regimen (p=0·061).

OUTCOME OF PREGNANCIES

Two women in the Yuzpe group continued their pregnancies and had vaginal deliveries of normal female infants. The other three had induced abortions. In the danazol group eight women had induced abortions and one delivered a normal male infant. Of the three women who got pregnant after taking mifepristone one continued her pregnancy and had a vaginal delivery of a normal male and two had induced abortions. The woman who was already pregnant when given the Yuzpe regimen had an induced abortion.

SIDE EFFECTS

Women in the Yuzpe group experienced more nausea and vomiting than those in the two others (table III). In the Yuzpe group 133 (70%) women experienced nausea, of whom 36 said it was severe. By comparison 58 (30%) of the women in the danazol group and 72 (37%) in the mifepristone group complained of nausea with only four (2%) and six (3%) women rating the symptoms as severe. The pattern for vomiting was similar. Almost a quarter (42) of the Yuzpe group experienced vomiting, of whom 12 (6%)

stated it was severe. One woman vomited so severely she was unable to take the second dose and resorted to an intrauterine device for postcoital contraception. Only six (3%) women in the danazol group and 5 (3%) in the mifepristone group experienced any vomiting. The only subject who had severe vomiting was the woman who developed an allergic reaction to danazol, which settled by the next day with no further treatment.

Breast tenderness was similar in all three groups (table III). A few women experienced other side effects including headache, tiredness, lethargy, and dizziness. None of these symptoms was rated as severe.

BLEEDING PATTERNS

Table IV shows the timing of bleeding relative to the expected first day of menstruation. Figure 3 shows the cumulative graph of time of bleeding relative to predicted day of next menstruation in each group. The Yuzpe regimen induced bleeding earlier, with 71 (38%) bleeding more than three days before the due date and only 12 (6%) bleeding more than three days late. Danazol had less effect on bleeding with 57 (30%) bleeding early and 17 (9%) bleeding late. In the mifepristone group 36 (19%) bled early and 73 (39%) bled late; 49 were at least a week late, of whom 15 were over 14 days late. In the mifepristone group 61 (32%) women bled more than three weeks after the unprotected intercourse compared with three (2%) in the Yuzpe group and 11 (6%) in the danazol group. Delayed bleeding seemed to cause anxiety, although this was partially allayed by measuring chorionic gonadotrophin concentration. Sixteen women had two bleeds, and it was impossible to tell clinically which one was their real period. This was seen slightly more often in the mifepristone group (nine; 5%) than in the danazol (three; 2%) or Yuzpe (four; 2%) groups.

TABLE III—*Side effects experienced in the first four days after taking treatment*

	No (%) of women receiving Yuzpe (n=191)	No (%) of women receiving danazol (n=193)	No (%) of women receiving mifepristone (n=197)
Nausea:			
None	58 (30)	135 (70)	125 (63)
Mild	49 (26)	40 (21)	44 (22)
Moderate	48 (25)	14 (7)	22 (11)
Severe	36 (19)	4 (2)	6 (3)
Vomiting:			
None	149 (78)	187 (97)	192 (97)
Mild	17 (9)	5 (3)	4 (2)
Moderate	13 (7)		1 (1)
Severe	12 (6)	1 (1)	
Breast tenderness:			
None	157 (82)	154 (80)	163 (83)
Mild	27 (14)	28 (15)	27 (14)
Moderate	7 (4)	9 (5)	7 (4)
Severe		2(1)	
Other side effects:			
No	186 (97)	192 (99)	194 (98)
Yes	5 (3)	1 (1)	3 (2)

TABLE IV—*Timing of menstruation after taking postcoital contraception*

Timing of menstruation relative to expected first day of period	No (%) receiving Yuzpe	No (%) receiving danazol	No (%) receiving mifepristone
<−7	42 (23)	21 (11)	10 (5)
−7 to −4	29 (16)	36 (19)	26 (14)
−3 to 3	95 (51)	107 (56)	69 (37)
4 to 7	9 (5)	7 (4)	24 (13)
>7	3 (2)	10 (5)	49 (26)
Bled twice (%)	4 (2)	3 (2)	9 (5)
Never bled* (%)	4 (2)	8 (4)	1 (1)
Total	186	192	188

*Four of the pregnant women experienced light bleeding during follow up and three women conceived after treatment and therefore did not bleed.

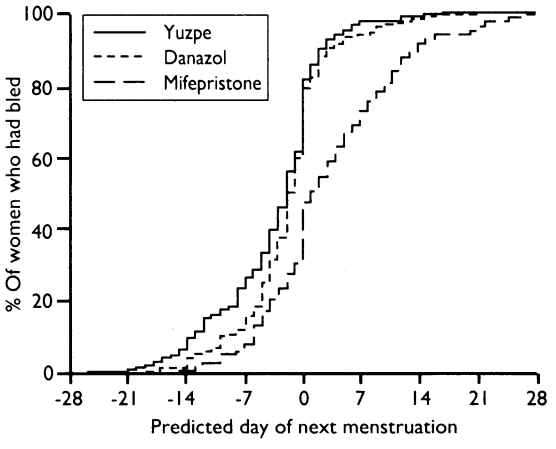

FIG 3—*Cumulative graph showing percentage of women having bled relative to predicted day of next due menstruation*

Discussion

Our results show that both the mifepristone and Yuzpe regimens are effective methods of postcoital contraception. In the Yuzpe group the risk of pregnancy was less than half of that predicted if no treatment were given and in the mifepristone group it was nil. The upper end of the 95% confidence interval was well below one in the mifepristone group, confirming its effect and only just above one in the Yuzpe group, suggesting it has a clinical effect.

Zuliani *et al* stated that danazol is a valid alternative to the Yuzpe regimen for postcoital contraception.[12] They showed significant efficacy against expected pregnancy rates with the Yuzpe regimen and with both 800 mg and 1200 mg of danazol (given in three doses). We found no significant difference between the observed and predicted pregnancy rates with danazol. The standardised ratio of 0·767 was below one but the confidence interval was wide. If current pregnancy rates are assumed the number of women recruited to the danazol group would have to be more than trebled before a significant effect could be established. Any biological effect of danazol seemed to be so small that we did not feel morally justified to continue this arm of the study; statistical proof would have required an unacceptably high number of observed pregnancies.

The mifepristone regimen was significantly more effective than both the danazol and the Yupze regimens. Differences between the Yuzpe and danazol groups were too small to establish significance.

SIDE EFFECTS AND BLEEDING PATTERNS

The Yuzpe method frequently produced side effects, which most women would rather avoid. Both mifepristone and danazol induced minimal side effects, which makes them more acceptable. Nevertheless, effectiveness is always the most important factor and allergy to danazol is possible.

A woman cannot be certain that she is not pregnant until she has had a normal bleed. The Yuzpe method tended to induce bleeding early so that only 12 (6%) women on this regimen were four or more days late and three (2%) were over seven days late. In the mifepristone group, however, 73 (39%) women bled more than three days late, of whom 49 were over seven days late.

Yuzpe *et al* reported that with their regimen 98·2% of women with regular cycles bled within three weeks of treatment.[3] In clinical practice this leads to a warning that the next period may be early, on time, or late but if there has been no proper bleeding three weeks after treatment a pregnancy test is advised. In our study that would have led to three women in the Yuzpe group but 61 in the mifepristone group needing a test. Women requesting postcoital contraception can

be assumed not to be, planning a pregnancy. A treatment which minimised the likelihood of a delayed bleed, and therefore the requirement for a pregnancy test, would seem advantageous. The three pregnancies conceived after mifepristone treatment suggests that the next cycle and ovulation may occur without an intervening bleed. As we found no true failures of mifepristone treatment it would seem reasonable to start hormonal contraception immediately after treatment. This would give good protection against unplanned pregnancy and obviate the need for pregnancy testing unless the withdrawal bleed after the first cycle of treatment is absent.

Conclusions

Most abortions in the Western World are carried out in young women, often early on in their sexual relationships. Knowledge and availability of postcoital contraception can reduce the numbers of unplanned pregnancies and give health professionals the opportunity to encourage and supply ongoing effective contraception.

We have shown that the mifepristone and Yuzpe regimens are effective. Mifepristone has greater effectiveness and fewer side effects but leads to greater disturbance of cycle and to difficulty in predicting risk of pregnancy until the following cycle. The Yuzpe method seems to be slightly less effective and has more side effects but rarely delays the next cycle. Danazol did not seem to be effective as postcoital contraception. The risk of pregnancy for each woman can be estimated reasonably accurately by careful questioning regarding the stage of the cycle and measurement of progesterone. To determine the relative usefulness and practical effectiveness of the Yuzpe and mifepristone regimens in clinical practice we suggest a large multicentre study including all women requiring postcoital contraception, even if their level of risk is difficult to determine.

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Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler

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Salmeterol is a long acting β_2 agonist used as a bronchodilator in asthma. Patients have been reported as suffering acute deteriorations in their asthma, often within minutes of exposure to salmeterol and against a background of stable asthma.[1] We report six cases of acute bronchospasm induced by inhaling salmeterol by metered dose inhaler but not by dry powder inhaler (diskhaler).

Patients, methods, and results

Five female and one male asthmatic patient (aged 17-48 years, mean 28) complained of breathlessness, wheeze, or cough after inhaling salmeterol. All subjects were taking inhaled salbutamol as necessary; five were taking regular beclomethasone, and one additional prednisolone. One subject took regular salmeterol (by diskhaler), one oral salbutamol, and one oral theophylline. Forced expiratory volume in one second at rest ranged from 69% to 105% of predicted values for age, sex, and height.

All subjects attended on three occasions, when they received two puffs of salmeterol or placebo by metered dose inhaler given double blind and in random order or salmeterol 50 μg by diskhaler. On two further visits four subjects received beclomethasone (Becotide) 100 μg and three salbutamol (Ventolin) 200 μg (given double blind in random order) (see figure). Intervals between treatments were 2-14 days. All subjects abstained from taking salmeterol for 24 hours and salbutamol for six hours before challenge. Forced expiratory volume in one second was measured before and at one, three, five, 10, 15, and 30 minutes after exposure.

Maximal percentage fall in forced expiratory volume in one second relative to baseline values was compared between treatments using Student's *t* test for paired samples.

The figure shows the changes in forced expiratory volume in one second after the different treatments. In all subjects forced expiratory volume in one second fell substantially after inhalation of either salmeterol (13·2% (SE 2·5%), p=0·005) or placebo (19·0% (3·2%), p=0·015) by metered dose inhaler. Two